Brownian Dynamics and Monte Carlo simulations, allowing us to integrate molecular-scale information, such as the shapes and sizes of each molecular species, into the rate equations of the model.The steady state cytoplasmic mRNA concentration shows several regimes with qualitatively different dependencies on the volume fraction ∃ ∴phi∃ of crowding agents, depending on the concentrations of the transcription factors, polymerases, and DNA binding sites. At physiologically realistic volume fractions, the mRNA output may be an increasing, decreasing, or non-monotonic function of ∃ ∴phi∃ in these various regimes. Our results suggest that the transcriptional output of a gene can be regulated jointly by the local level of macromolecular crowding, together with the local concentrations of polymerases and DNA-binding proteins.

1906-Pos Board B636
Crosstalk and the Evolution of Specificity in Two-Component Signaling
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Two-component Signaling (TCS) serves as the dominant signaling modality in bacteria. A typical pathway includes a sensor Histidine Kinase (HK) that phosphorylates a Response Regulator (RR), modulating its activity in response to an incoming signal. Most HKs are bifunctional, acting as both kinase and phosphatase for their substrates. Unlike eukaryotic signaling networks, there is very little crosstalk between bacterial TCS pathways; indeed, adding crosstalk to a pathway can have disastrous consequences for cell fitness. It is currently unclear exactly what feature of TCS necessitates this degree of pathway isolation. In this work we used mathematical models to show that, in the case of bifunctional HKs, adding a competing substrate to a TCS pathway will always reduce response of that pathway to incoming signals. We found that the pressure to maintain cognate signaling is sufficient to explain the experimentally observed ''kinetic preference'' of HKs for their cognate RRs. These findings imply a barrier to the evolution of new HK-RR pairs, since crosstalk is unavoidable immediately after the duplication of an existing pathway. We characterized a set of ''near-neutral'' evolutionary trajectories that minimize the impact of crosstalk on the function of the parental pathway. These trajectories predicted that crosstalk interactions should be removed before new input/output functionalities evolve. Analysis of HK sequences in bacterial genomes provided evidence that the selective pressures on the HK-RR interface are different from those experienced by the input domain immediately after duplication. This work thus provides a unifying explanation for the evolution of specificity in TCS networks.

1907-Pos Board B637
Heterogeneous Protein-Protein Interaction Systems Modeled using a New Integrator for Single-Particle Reaction Diffusion
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Proteins perform functions ranging from signal transmission and transcriptional regulation to assembly into structural scaffolds by stochastically binding with one another in the cellular environment. Approaches to modeling these processes at a scale capable of capturing the dynamics of whole populations of proteins vary in the degree of spatial resolution and the rules describing the interactions between proteins. We present here a new algorithm for simulating both the spatial and temporal evolution of protein interactions by rigorously solving reaction-diffusion equations at single-particle resolution. Our algorithm is designed to be both highly accurate and relatively simple to implement, making it applicable to large and heterogeneous systems, including those arising in systems biology applications. In our approach we combine the use of the exact Green's function for a pair of reacting particles with the approximate free diffusion propagator for position updates to particles. Through the use of a trajectory reweighting scheme our method recovers the exact association rates for a pair of interacting particles at all times. As a result, simulations of many-body systems with our method quite accurately reproduce the theoretically known dynamic behavior for a variety of different reaction types. This approach has applications in modeling pathways and networks of protein driven processes where reactions can range widely in strength and thousands of proteins may participate. With a limited amount of bookkeeping necessary to ensure proper association rates for each reactant pair, our approach can adapt to changes to reaction rates or diffusion constants as a result of reaction events. The formalism can also be extended to physical descriptions of protein interactions that incorporate long-range forces or orientational constraints, providing a framework to help bridge the gap between molecular models and particle-based models of protein interactions.

1908-Pos Board B638
Computational Model for Cell Shape Regulation through Mechanosensing and Mechanical Feedback
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In response to both intracellular and extracellular signals, cells undergo controlled changes in morphology, which form a fundamental step in many developmental processes, including tissue morphogenesis and organogenesis. These changes require a means for sensing and interpreting the signaling cues, for generating the forces that act on the cell's physical material, and a control system that regulates this process. Identifying the molecular mechanisms that drive and regulate cell shape changes is a great challenge in the field of cell biology.
In studies of dividing Dictyostelium discoideum amoebae, it has been shown that force-generating proteins could be localized in response to external mechanical perturbations. This mechanosensing, and the ensuing mechanical feedback, is believed to play an important role in minimizing the effect of mechanical disturbances during cell division. Owing to the complexity of the feedback system, which couples mechanical and biochemical signals involved in shape regulation, it is essential to develop theoretical approaches that can guide further experimentation and investigation.
Here, we present a mechano-chemical computational model that explains the different mechanosensory and mechanoresponsive behaviors observed in Dictyostelium cells.
This model expands a multi-scale myosin bipolar thick filament assembly model that incorporates cooperative and force-dependent myosin-actin binding, by identifying the feedback mechanisms hidden in the observed mechanoresponsive behaviors (monotonic vs. oscillatory) of Dictyostelium cells in the micropipette aspiration experiments. By doing so, we can explain the mechanism behind different modes of cellular retraction and hence cell shape regulation.

1909-Pos Board B639
Stochastic Modelling of Gene Regulatory Mechanisms in PTEN Dynamics: Does Space Matter?
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Stochastic simulation has proven to be an invaluable tool for modelling biological processes involving small numbers of molecules, such as proteins and messenger RNA (mRNA). One aspect of sub-cellular dynamics that is often overlooked in stochastic models is the effect of spatial constraints on the behaviour of a cell; cellular processes depend not only on the number of molecules present, but also on their distribution, how they move within the cell and how they interact with each other. This type of modelling is particularly relevant in crowded media such as the cytoplasm, which is filled with organelles and other molecules. For these reasons, we hypothesise that spatially-resolved models of cells will prove to be more effective at simulating the behaviour of individual cells than spatially-averaged ones. To test this hypothesis, we studied the regulation of the mRNA of the tumour suppressor gene, PTEN, by a group of small RNAs called microRNAs. We created spatially-resolved models of the system using Smoldyn, a discrete-time, continuous-space, agent-based spatial stochastic simulation tool, and compared the results with those obtained using the spatially-averaged stochastic simulation algorithm (SSA). We measured the average time for an mRNA to be degraded or repressed by a threshold number of microRNA, and investigated the change in this mean time with the inclusion of cytoplasmic obstructions, non-uniform distributions of molecules, and competition for binding by competing endogenous RNAs (ceRNAs). Preliminary results demonstrate a considerable impact of spatial modelling on observed cellular response times, as we see a dramatic increase (>100-fold) in the time taken for microRNAs to locate mRNA binding sites in the spatially-resolved model.

1910-Pos Board B640
Bacterial Growth and Division: Theory
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Minimal models reveal principles behind cellular functions, such as, what biophysical rules underlie growth limits? how ribosomes and metabolic proteins compete for energy resources? how are efficiency of conversion of energy to mass compete with growth rate following economic principles? To address

these questions we develop a reaction based minimal model of the exponentially growing E. coli in a glucose medium.

1911-Pos Board B641

Computational Modeling Predicts Phosphatase Oxidation as an Important Axis of Redox Regulation in IL-4 Signaling

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Reactive oxygen species (ROS) are produced following activation of several types of cell surface receptors and can play an important role in modulating cell signaling. How simultaneous oxidative modifications of multiple proteins, sometimes with potentially opposite effects, regulate cell signaling is not well understood at the system level. We are using computational modeling based on quantitative experimental measurements to develop a systemic understanding of redox regulation of cell signaling in the context of the IL-4 signaling pathway. We observe that IL-4 signaling in Jurkat cells is accompanied by transient ROS production, and ROS augment signaling activity as measured by STAT6 phosphorylation. A number of candidate redox-regulated mechanisms exist in the IL-4 pathway that could contribute to the observed outcomes; however, it is technically challenging to directly measure redox modifications of the possibly redox-regulated proteins. To circumvent this issue, we have developed kinetic models of IL-4 signaling that incorporate competing hypotheses regarding redox regulatory mechanisms. With the guidance of measurable experimental data we are using innovative model selection strategies to determine the best candidate models. We have also acquired time course data for processes not directly related to redox regulation, such as transcriptional negative feedback regulation and proteasomal degradation as mechanisms for downregulating IL-4 signaling, that aid model selection and validation. Our results so far indicate that reversible oxidative inhibition of phosphatases and compartmentation of phosphatase activity between subcellular compartments may be the primary redox regulatory mechanisms in IL-4 signaling. These studies will help evolve an understanding of how oxidative modifications of different components of the signaling pathway operate in parallel along with better studied post-translational modification mechanisms of protein regulation to determine the overall dynamics of cell signaling.

1912-Pos Board B642

Multi-Finite Buffer Method for Direct Solution of Discrete Chemical Master Equation

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Many biological reaction networks are intrinsically stochastic due to random thermal fluctuations. Stochasticity is significant when the copy number of participating molecular species are small. The discrete Chemical Master Equation (dCME) provides a general framework to study the underlying stochastic processes of biological networks. Although the direct solution of dCME is advantageous over approximation methods such as the Langevin and the Fokker-Planck equations, it is challenging to obtain exact solution to the dCME. The Finite Buffer dCME Method provides an optimal algorithm to enumerate the underlying state space, and has been used to compute the exact solutions of dCME for several problems. In this study, we extend the finite buffer method by introducing multiple buffer queues for more effective construction of the state space and for quantitative control of errors, when buffer sizes are limited. By introducing the concept of open Independent Birth-Death (IBD) units, which are non-intersecting sets of reactions grouped by common synthesis and degradation reactions, we can enumerate the state space optimally and assess errors for each open IBD from the probability of buffer depletion, when the buffer size is limited. We also describe theoretical estimation of the error bound for any given buffer size of an IBD, so its buffer size can be optimized. We demonstrate the effectiveness of our approach in computing time-evolving and steady state probability landscapes, as well as first passage time distribution using the birth-death process, the bistable Schlogl model, the bistable toggle switch model, and the phage lambda lysogenic-lytic switching model as examples. We also compare our results with those using other methods.

1913-Pos Board B643

Optimized Energy Dissipation of Minde Oscillator for Symmetric Cell Division

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Prokaryotic cells often utilize a MinCDE oscillatory system to locate the mid-cell location for symmetric cell division. Several diffusion-reaction based models have been developed to explain the occurrence of the sustainable oscillation of Min proteins from pole to pole, and extensive efforts have been devoted to understanding the patterns of oscillation and the precision of the designated mid-cell location. However, how this highly dissipative yet vital biological oscillation is driven by energy-bearing molecules is left uninvestigated. We address this fundamental question by studying the MinCDE oscillator in *Escherichia coli*. We assess the oscillator's performance of spatially differentiating mid-cell region from the rest of cell body, and further relate this quantified performance to the amount of dissipated energy as well as the stage of cell growth. Unlike the two adaptive reaction networks (Negative-Feedback-Loop and Feedfoward-Loop) whose performances get monotonically improved upon larger energy input, the MinCDE oscillator shows nonmonotonic performance-to-cost relation that depends on the reaction rates and the cell length. Our analysis further indicated that this oscillator operates optimally at cell length around 4 micro-meters and to achieve the best performance, energy is dissipated unevenly through the reaction pathway with the largest dissipation at immobilizing MinD and hydrolyzing ATP. These results present a novel mode of converting biochemical energy into spatiotemporal information in living systems and suggest that the MinCDE oscillator in prokaryotic cells are highly optimized both functionally and energetically to ensure high fitness under natural selection.

1914-Pos Board B644

Construction of a Self-Consistent Landscape for Multistable Gene Regulatory Circuits

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Cell fate decisions during embryonic development and tumorigenesis pose a major research challenge in modern developmental and cancer biology. Cell fate decisions between different phenotypes (e.g. epithelial, mesenchymal and epithelial/mesenchymal hybrids) are regulated by multistable gene circuits that give rise to the coexistence of several stable states (phenotypes). Internal and external noise play crucial role in determining the transitions between and the relative stability of the coexisting phenotypes. The deterministic dynamics of these circuits is not derivable from a potential. Yet, motivated by Waddington Epigenetic Landscape, many rely on the notion of effective potential to describe cell fate determination in the presence of noise. Here, we present a construction of a self-consistent landscape (effective potential, W = -ln(probability)), utilizing the Eikonal equation approach (WKB approximation of the corresponding Fokker Planck equation) for the cases of white noise and shot noise. The approach is based on utilizing the method of characteristics in a special way, which is illustrated for the concrete examples of the bistable and tristable double inhibition circuits. We also deviced a numerical method to efficiently calculate the contour of the potential and the optimal path for the transitions from one stable state to another. We tested the method on the bistable and tristable double inhibition circuits, and we showed that the constructed landscape agrees very well with the numerical simulation of the stochastic equations. We expect this method to be valuable to a wide range of multistable gene circuits.

1915-Pos Board B645

Multistability in GTPase-Based Decision Circuits

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Cell fate decisions during embryonic development and tumorigenesis pose a major research challenge in modern developmental and cancer biology. Cell fate decisions between different phenotypes are regulated by multistable gene circuits that give rise to the coexistence of several stable states (phenotypes). GTPases are molecular switches, which toggle between GTP-bound active state and GDP-bound inactive state. GTPase-based gene regulatory circuits play a crucial role during embryonic development and tumorigenesis. An archetypal example is the RhoA-Rac1 circuit that regulates cell fate determination between amoeboid and mesenchymal phenotype. Here, we introduced a biologically consistent, yet tractable, theoretical framework to model and investigate GTPase-based gene regulatory circuits. We show that although the modeling approach incorporates the details of GTPase activation/inactivation dynamics (GTP loading and hydrolysis reactions), it yields relatively simple effective circuit models. The efficiency of this new approach is illustrated for the specific case of the Rac1-RhoA mutually inhibitory feedback loop. We found that this simple two components unit can yield, for realistic circuit